



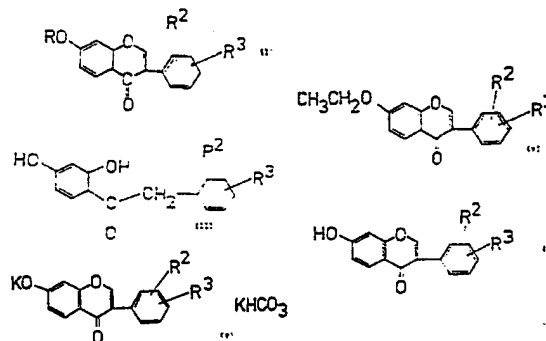
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/HU90/00023 (22) International Filing Date: 6 April 1990 (06.04.90) (71) Applicant (for all designated States except US): CHINOIN GYÓGYSZER- ÉS VEGYÉSZETI TERMÉKEK GYÁ- RA RT. [HU/HU]; Tó utca 1-5, H-Budapest IV (HU). (72) Inventors; and (75) Inventors/Applicants (for US only) : KÁLLAY, Tamás [HU/ HU]; Gépmadár u. 16, H-1106 Budapest (HU). LÁNYI, György [HU/HU]; Kalló esp. u. 10, H-1124 Budapest (HU). LEDNICZKY, László [HU/HU]; Üllői u. 66/B, H-1082 Budapest (HU). IMREI, Lajos [HU/HU]; Meuthner S. u. 143, H-1131 Budapest (HU). HOFF- MANN, György [HU/HU]; Herzen u. 5, H-1136 Budap- est (HU). SZILADI, Mária [HU/HU]; Attila u. 12, H- 1152 Budapest (HU). SOMFAI, Éva [HU/HU]; Tancs- sics u. 8, H-1018 Budapest (HU). MONTAY, Tibor [HU/HU]; Baross u. 123, H-1089 Budapest (HU).		(74) Agent: DANUBIA; P.O. Box 198, H-1368 Budapest 5 (HU). (81) Designated States: AT (European patent), AU, BE (Euro- pean patent), CA, CH (European patent), DE (Euro- pean patent)*, DK (European patent), ES (European pat- ent), FI, FR (European patent), GB (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), NO, SE (European patent), SU, US. Published With international search report.

(54) Title: AN IMPROVED PROCESS FOR THE PREPARATION OF SUBSTITUTED ISOFLAVONE DERIVATIVES

(57) Abstract

The invention relates to a process for the preparation of pure isoflavone derivatives of general formula (I), wherein R stands for hydrogen or isopropyl, R² and R³ stand for hydrogen or C₁₋₂ alkoxy by reacting a rezorcinol-derivative of general formula (III) wherein R² and R³ are as given above with ethyl-orthoformate of the formula (IV): (C₂H₅O)₃CH in the presence of a base and optionally by alkylating the product. The process is carried out by subjecting the compounds of general formula (III) and (IV), wherein R² and R³ are as given above, to ring-closure at 70-100 °C in the presence of an organic solvent, preferably dimethyl-formamide and/or isopropanol in a 0.3-2-fold volume calculated to the volume of the rezorcinol derivatives and/or in the presence of excess of the ester of formula (IV) in order to produce a 20-70 % by weight solution (supersaturated) of the product of general formula (VII) wherein R² and R³ are as given above, and whereby the product of general formula (VII), wherein R² and R³ are as given above, continuously precipitates from the mixture and filtering the product of general formula (VII) after cooling from the reaction mixture and/or adding a polar or apolar solvent to the reaction mixture and selectively dissolving thus the side product and filtering the product of general formula (VII), wherein R² and R³ are as given above, and/or adding to the reaction mixture an almost equivalent amount of anhydrous potassium carbonate and isolating the crystallized double salt of general formula (V) wherein R² and R³ are as given above, whereafter the products of general formula (V) or (VII) are reacted with isopropyl-halide and optionally separating the pure product containing at most 0.5 % by weight of contaminating compound of general formula (VI).



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An improved process for the preparation of substituted
isoflavone derivatives

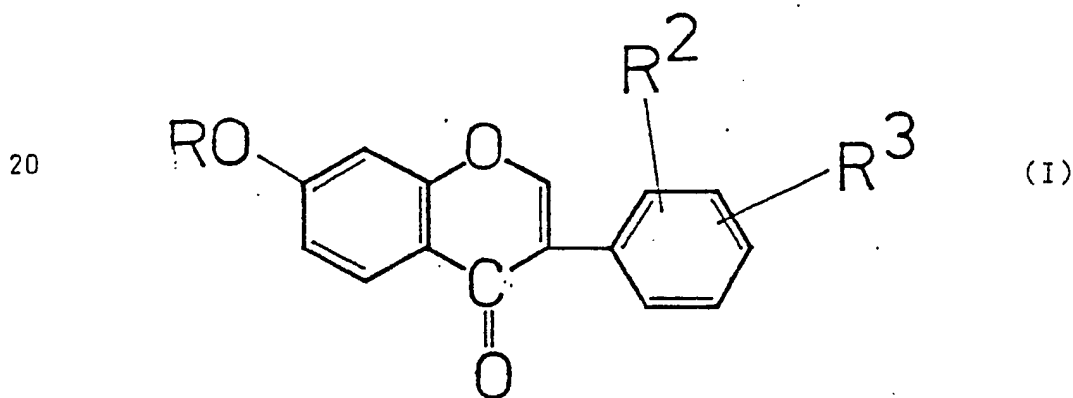
The present invention relates to an improved
5 process for the preparation of substituted isoflavone
derivatives of high purity, which are suitable for
the preparation of pharmaceutical compositions, particu-
larly for the preparation of ipriflavon (Osteochin^R)
which is the common name of 7-isopropoxy-isoflavone
10 suitable against osteoporosis (HU-PS 162 377).

In the specification the substituents are defined
as follows:

R stands for hydrogen or isopropyl;

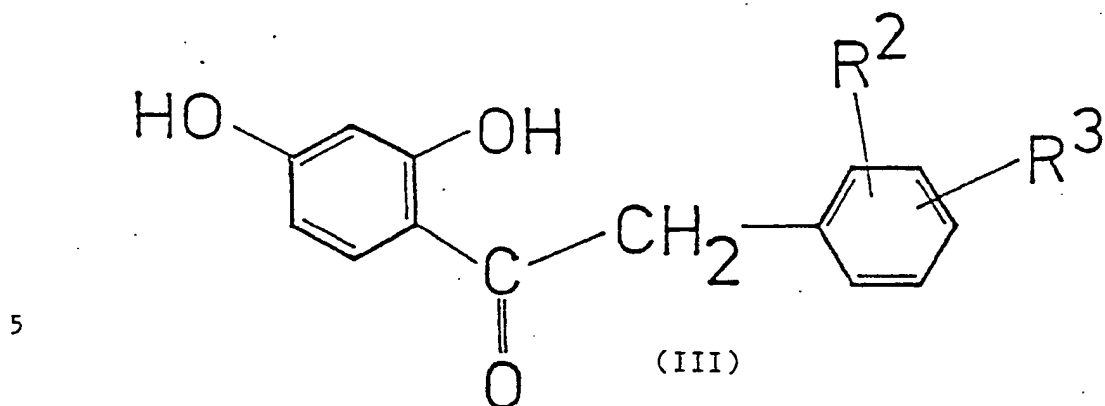
R² and R³ stand for hydrogen or C₁₋₂alkoxy.

15 According to the invention pure isoflavone deriva-
tives of the general formula (I)

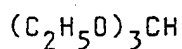


25 can be prepared by reacting rezorcinol-derivatives
of the general formula (III)

- 2 -



and ethyl-ortho-formiate

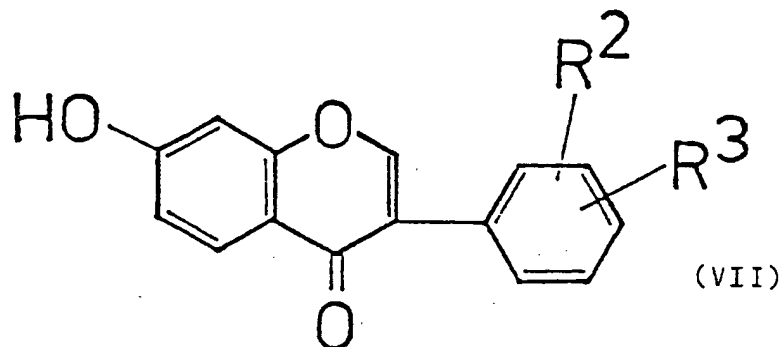


(IV)

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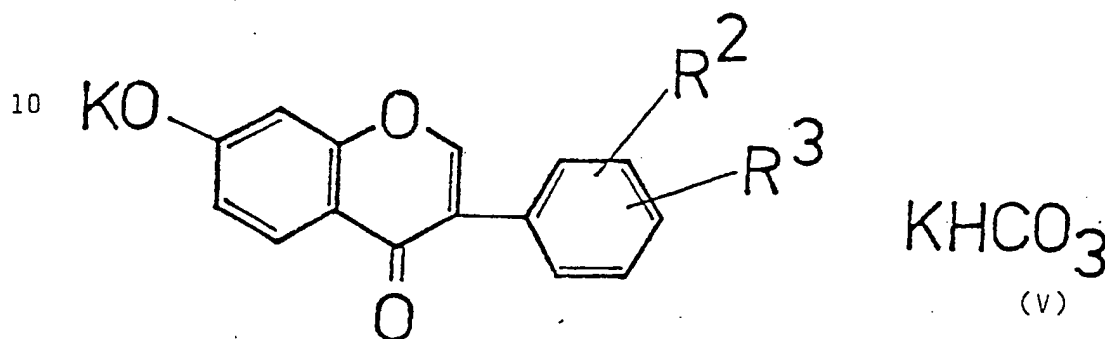
in the presence of a base and optionally by alkylating the products whereas the compounds of the general formula (III) and (IV) are subjected to ring closure in the presence of an organic solvent, preferably dimethyl-
 15 formamide and/or isopropanol and/or in a 0.3 - 2-fold volume calculated to the volume of the resorcinol derivatives of the general formula (III) and/or in the presence of excess ester of the formula (IV) at a temperature of 70-100 °C, whereupon the reaction mixture becomes
 20 supersaturated (20-70 % by weight) related to the product of the general formula (VII)

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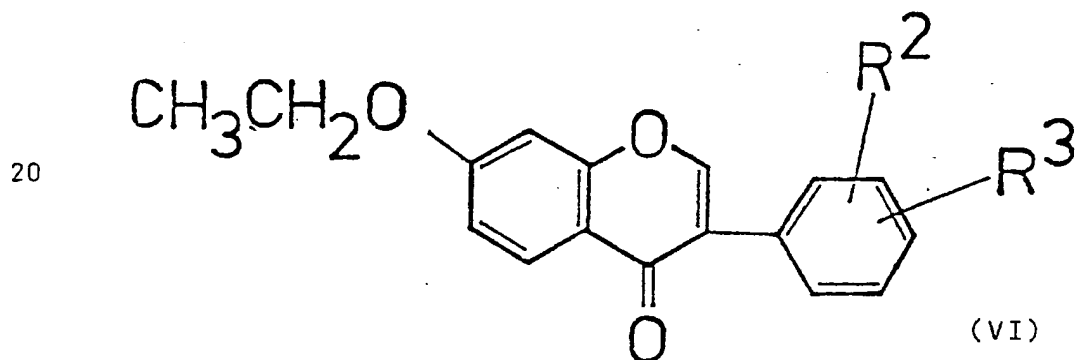


and thus the product of the general formula (VII) conti-

nuously precipitates from the reaction mixture in the course of the reaction. After cooling the reaction mixture the product of the general formula (VII) is filtered without or with the addition of a solvent or
5 an almost equivalent amount of anhydrous potassium carbonate is added and the crystallizing double salt of the general formula (V)



15 is isolated while the contamination of the general formula (VI)



25 remains in the solution, respectively it dissolves selectively, whereafter the product of the general formula (V) or (VII) is reacted with isopropyl halide and the pure product containing up to 0.5 % by weight of the contamina-

tion of the general formula (VI) is optionally separated.

As it is known, the appropriately substituted 7-hydroxy-isoflavone-derivatives are suitable intermediates in the synthesis of 7-alkoxy-isoflavones which are effective medicines in human and veterinary therapy. Thus, it is desirable to prepare the 7-hydroxy-isoflavone-derivative of the general formula (VII) in such chemical purity that it should be suitable for the preparation of the 7-alkylated end-product in appropriate purity, that is, it is an important requirement to suppress the formation of the contaminating derivatives of the general formula (VI).

The 7-hydroxy-derivative of the general formula (VII) can be prepared in the industry by subjecting the resorcinol-derivative of the general formula (III) and an orthoformic acid ester of the general formula (IV) to ring closure. The following methods are known for carrying out the above synthesis:

In a pyridine-piperidine mixture by boiling for 1 hour (CA. 56, 2408) with a yield of 80 % with 70 % perchloric acid or POCl_3 -dimethyl-formamide (Zsurn. Chem. Khim. 1970 40/2459; CA 75. 201219), with a yield of 33 % using HCl as a catalyst (CA. 83, 193010), with a yield of 70 %. In an analogous process the mixture is boiled for 8 hours in pyridine/piperidine mixture and unsubstituted isoflavone is prepared with a yield of 60 % starting from 2-hydroxy-phenyl-benzyl-ketone (US-PS 3 340 276).

The mentioned ring closures are all performed at 110 - 150 °C in the presence of a mixture of a solvent boiling at a temperature above 100 °C (pyridine homologue, dimethyl-formamide etc.) and a secondary amine (piperidine, morpholine, pyrrolidine) preferably at the boiling point of the mixture. In some cases the formed alcohol is distilled off during reaction, presumably in order to improve conversion or in order to raise temperature.

When reproducing said processes we have found that next to 7-hydroxy-isoflavone derivatives of the general formula (VII) a significant amount (in some cases 2 - 10 % by weight measured by HPLC) of 7-ethoxy-isoflavone-derivative of the general formula (VI) is formed next to other side products. By reducing the molar excess of ethyl-orthoformate the yield is significantly reduced but the 7-ethoxy-isoflavone contamination can not be eliminated. The 7-hydroxy-isoflavone-derivative of the general formula (VII) prepared by this method can be purified only by an expensive method using several solvent treatments.

We have found that unlike the reaction disclosed in the literature a moderate ring closure can be used so that the formed 7-hydroxy-isoflavone of the general formula (VII) starts to crystallize from the reaction mixture shortly after the reaction is initiated.

The pure 7-hydroxy-isoflavone derivatives of the general formula (VII) isolated from the reaction mixture contain such a small amount of contamination

of general formula (VI) (about 0.1 - 0.5 % by weight measured by HPLC method) and other side-products which can be eliminated if desired by one single purification step.

5 We have further found that the contamination of the general formula (VI) can be removed from the product by isolating a novel potassium-double salt.

When performing the ring closing reaction one may preferably proceed by performing the reaction at
10 80 - 90 °C and using a heat treatment for 6 - 10 hours. It is further preferred to promote the supersaturation by retaining ethanol formed in the reaction during the ring closure. It is further preferred to use a base catalyst for the ring closure, such as a secondary
15 amine, preferably morpholine, piperidine or pyrrolidine.

During ring closure we found most preferable to react a ketone of the general formula (III) with 20 % by mole excess of orthoformic acid ester and a 0.3-2-fold amount of solvent and about 20 % by mole of a
20 secondary amine at 80 - 90 °C. After about 30 - 60 minutes 7-hydroxy-isoflavone of the general formula (VII) starts to crystallize from the reaction mixture. The reaction is continued until the complete conversion of the starting ketone of the general formula (III).
25 Yield is above 90 %, and the obtained product contains a contamination of the general formula (VI) in less than 0.1-0.5 % by weight shown by HPLC method.

The double salt of the general formula (V) is

formed from the reaction mixture by using an apolar solvent, preferably toluene with an anhydrous potassium carbonate at 40 - 80 °C, preferably at 60 °C. By isolating a double salt a further purification and separation, respectively, is conducted. The double salt can be directly alkylated with alkyl-halide, without an acid-binding agent in a suitable solvent, such as dimethyl formamide or ketone. Thus, 7-isopropoxy-isoflavone derivatives can be obtained in a pure state.

10 The final step of the process according to the invention is the optional alkylation of the pure 7-hydroxy-isoflavone. The alkylation can preferably be carried out in the presence of a potassium carbonate acid-binding agent in acetone or dimethyl-formamide medium with alkyl-bromide. Under suitable conditions the product obtained after ring-closure contains less than 0.1 % by weight of 7-ethoxy-isoflavone and this product can be used for preparing pharmaceutical compositions.

20 Further advantages of the process according to the invention are:

- that the process ensures a yield higher than 10 % related to the method used in the literature;
- a particularly pure chemical can be obtained, which is

25 of pharmaceutical quality.

 The further details of the invention are illustrated by the following examples.

Example 1

62.5 g (0.274 mole) of 2,4-dihydroxy-phenyl-
-benzyl-ketone, 105 ml of isopropanol, 5 ml of morpholine
and 49,7 g (0.33 mole) ethyl-ortoformiate are stirred
5 for 7 hours at 80 - 90 °C. During the reaction in the
first half hour the crystals start to precipitate.
At the end of the reaction the crystalline suspension
is cooled to -5 °C and filtered. After drying 59.1 g
of 7-hydroxy-isoflavone are obtained.

10 Yield: 90.6 %.

The active ingredient content of the product is above
98 % by spectroscopy.

7-ethoxy-isoflavone contamination by HPLC method:
0.2-0.4 % by weight.

15 Example 2

We proceed as disclosed in example 1. When the
reaction is completed 50 ml of solvent are distilled
off from the crystalline suspension and 160 ml of metha-
nol are added under stirring. The mixture is stirred at
20 58 - 60 °C for 20 minutes, whereafter it is crystallized
at -5 °C. The precipitated substance is filtered and
dried. 58.8 g of 7-hydroxy-isoflavone are obtained.
Yield: 90.1 %. Active-ingredient content is above 98 %
(by spectroscopy).

25 Contamination of 7-ethoxy-isoflavone by HPLC method:
0.2 -0.3 % by weight.

Example 3

90 ml of solvent are distilled off the reaction

mixture as obtained in Example 1, whereafter 37.8 g (0.274 mole) of anhydrous potassium-carbonate and 200 ml of toluene are added, and the reaction mixture is stirred for 30 minutes at 60 - 65 °C followed by stirring at 0 - (-5) °C for 2 hours. The double salt containing 7-hydroxy-isoflavone-potassium salt and potassium-hydrogen-carbonate is filtered and dried. 98.5 g of a double salt is obtained.

Yield: 95 %.

10 Analysis: $C_{15}H_9O_3K.KHCO_3$ Molecular weight: 376

	Calculated	Found
C%	51.06	51.9
H%	2.66	2.76
15 K%	20.7	21.8

NMR by BRUKER WP-80 spectrophotometer in DMSO- d_6 solvent by using a TMS inert standard

20	1H	"double salt"	7-hydroxy-isoflavone
	5 C-H	7.50 ppm (d) $^3J = 9$ Hz	8.00 ppm (d) $^3J = 9$ Hz
	6 C-H	6.13 ppm (dd)	6.90 ppm (dd)
	8 C-H	5.77 ppm (d) $^4J = 2$ Hz	6.87 ppm (d) $^4J = 2$ Hz
25	^{13}C		
	7 C	174.93 ppm	156.82 ppm

The obtained double-salt is dissolved in a three-fold amount of methanol and water at 50 - 60 °C. The solution is clarified and filtered. The pH value of the filtrate is adjusted to 1 by using an 1:1 dilution of aqueous hydrochloric-acid, the precipitated material is filtered, washed to neutral and dried. 58.7 g of 7-hydroxy-isoflavone are obtained. The product contains 98 % by weight of pure product by spectroscopy. 7-ethoxy-isoflavone content by HPLC method: 0.1 % by weight.

Yield: 90 %.

Example 4

50 g (0.219 mole) of a mixture of 2,4-dihydroxy-phenyl-benzyl-ketone, 20 ml of dimethyl-formamide, 2.6 ml of morpholine and 39.06 g (0.26 mole) of ethyl-orthoformate is stirred for 7 hours at 80 - 90 °C. After 25 minutes crystallization can be observed. At the end of the reaction time the crystallized suspension is diluted with 120 ml of chloroform and it is crystallized at 0 °C for 2 hours. After filtration the product is covered twice with 45 ml of chloroform and dried. 47.9 g of 7-hydroxy-isoflavone are obtained.

Yield: 91.9 %.

7-ethoxy-isoflavone contamination by HPLC method:
0.1 - 0.3 % by weight.

Example 5

25 g (0.1096 mole) of a mixture of 2,4-dihydroxy-phenyl-benzyl-ketone, 12.5 ml dimethyl-formamide, 2 ml of piperidine and 19.7 g (0.133 mole) of ethyl-

-orthoformate is stirred for 16 hours at 80 - 90 °C and diluted with 65 ml of chloroform. The precipitated substance is isolated and boiled with an 8:1 mixture of chloroform:methanol and it is filtered and dried.

5 23.5 g 7-hydroxy-isoflavone are obtained.

Yield: 90 %.

Product-content by spectroscopy: 98.5 % by weight.

7-ethoxy-isoflavone content: 0.2-0.4 % by weight (HPLC).

Example 6

10 A mixture of 20 g (0.0877 mole) 2,4-dihydroxy-
-phenyl-benzyl-ketone, 20.7 g (0.14 mole) ethyl-ortho-
formiate and 1 ml of morpholine is stirred on a hot
water bath. Crystallization starts after heating for
25 minutes. The inert temperature falls back to 87 °C
15 from 96 °C during the reaction. After stirring for 5
hours the reaction mixture is diluted with 48 ml of
chloroform and then one may proceed as disclosed in
Example 5. 18.9 g of 7-hydroxy-isoflavone are obtained.
Yield: 90.6 %. Content by spectroscopy: 99 % by weight,
20 7-ethoxy-isoflavone content: 0.1 - 0.2 % by weight (HPLC).

Example 7

A mixture of 100 kg (438.5 mole) of 2,4-dihydroxy-
-phenyl-benzyl-ketone, 38 kg of dimethyl-formamide,
5.2 kg of morpholine and 75 kg (506 mole) of ethyl-
25 -orthoformiate is stirred at 80 - 90 °C, while within
one hour crystallization is initiated. 360 kg of chloro-
form are added to the suspension after 7 hours at 60 °C.
After cooling the crystalline substance is centrifuged,

covered with chloroform, filtered and dried. 94.5 kg of 7-hydroxy-isoflavone are obtained, 7-ethoxy-isoflavone content: 0.1 % by weight, yield: 90.5 %.

Example 8

5 98.5 g of double salt are suspended in 100 ml of dimethyl-formamide. 44 g (0.36 mole) isopropyl-bromide are added, and the reaction mixture is stirred at 75-80 °C for 2 hours and then poured on 250 ml of water. The precipitated substance is filtered, washed with water
10 to neutral and dried at 60 °C. 66 g of 7-isopropoxy-isoflavone are obtained, active ingredient content: 99.5 %, drying loss is 0.1 %, 7-ethoxy-isoflavone-content: 0.1 %. Yield: 86.1 %, calculated to 2,4-dihydroxy-phenyl-benzyl-ketone.

15 Example 9

14.4 g (0.05 mole) of 2,4-dihydroxy-phenyl-(3',4'-dimethoxy-benzyl)-ketone are reacted with 10.5 g (0.07 mole) ethyl-ortoformiate in 10 ml of dimethyl-formamide in the presence of 1 ml morpholine. The reaction mixture
20 is maintained at 80 - 85 °C, and in the second hour a solid precipitates. After 6 hours 100 ml of chloroform are added to the mixture, the precipitated substance is filtered and dried. 7-hydroxy-3',4'-dimethoxy-isoflavone is obtained.

25 Mp.: 259 - 262 °C.

After recrystallization from dimethyl-formamide the product melts at 263 - 264 °C.

Analyses: $C_{17}H_{14}O_5$ Molecular weight: 298
calculated: C % = 68.46 % H % = 4.69 %;
found: C % = 68.30 % H % = 4.72 %.

The product is identical according to NMR test.

5 Thin layer chromatography:

developing system: toluene:n-butyl-acetate-acetic-
-acid = 8:2:1

Adsorbent: Kieselgel 60 F₂₅₄ (Merck)

Application: 0.2 g (10 ml dimethyl-formamide 100 μ g)

10 Front: 16 cm

Development: in UV light at 254 nm

Rf = 0.4.

Example 10

15 47.4 g (0.15 mole) 2,4-dihydroxy-phenyl-3,4-
-ethoxy-benzyl-ketone are reacted with 31.5 g (0.21 mole)
ethyl-orthoformate in 20 ml of dimethyl-formamide in
the presence of 3 ml morpholine. The reaction mixture is
maintained at 80 - 85 °C for six hours. Upon cooling to
20 60 °C 100 ml of chloroform are added. The precipitated
substance is filtered and dried. Product: 7-hydroxy-
-3',4'-diethoxy-isoflavone.

M.p.: 189 - 191 °C.

After recrystallization from dimethyl-formamide:

25 m.p.: 192 - 193 °C.

Analysis for the formula $C_{19}H_{18}O_5$:

calculated: C % = 69.93; H % = 5.52;

found: C % = 69.31; H % = 5.63.

Molecular weight: 326.

Identical according to NMR analysis.

Thin layer chromatographical test: see example 8.

Rf = 0.5.

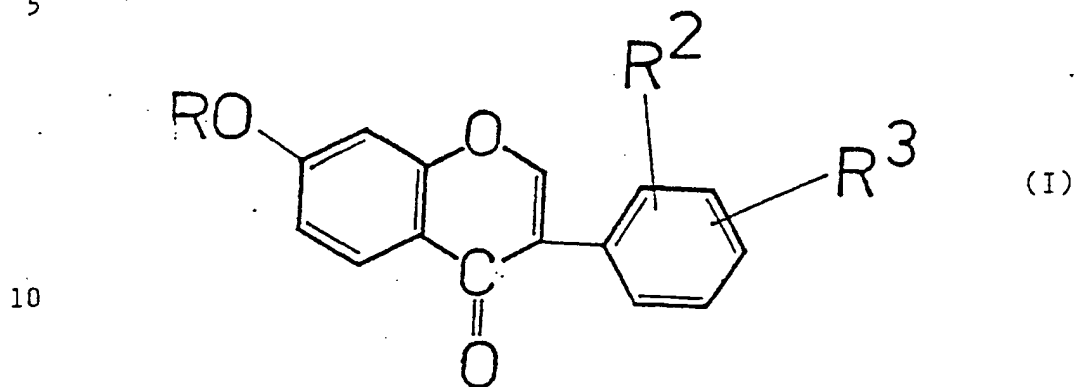
5 **Example 11**

A mixture of 75 kg dimethyl-formamide, 100 kg (420 mole) of 7-hydroxy-isoflavone and 76 g (550.7 mole) anhydrous potassium carbonate and 73 kg (598.3 mole) of isopropyl bromide are reacted at 75 - 95 °C for 2
10 hours, and the mixture is maintained for 10 minutes at 100 °C. To the reaction 45 kg of isopropanol and 350 kg of water are added under cooling. The crystal suspension is filtered and washed to neutral at 25 °C. The wet product is crystallized in a 4.4-fold amount
15 of anhydrous ethanol calculated to the dry substance content. The product is filtered with ethanol and dried at 60 °C.
112.9 kg of 7-isopropoxy-isoflavone are obtained.
M.p.: 118 - 119 °C.
20 Active ingredient content: above 99.8 % (HPLC), 7-ethoxy-isoflavone content: less than 0.1 % and it does not contain contamination.
Yield: 96 %.

Claims

1. Process for the preparation of pure isoflavone derivatives of the general formula (I),

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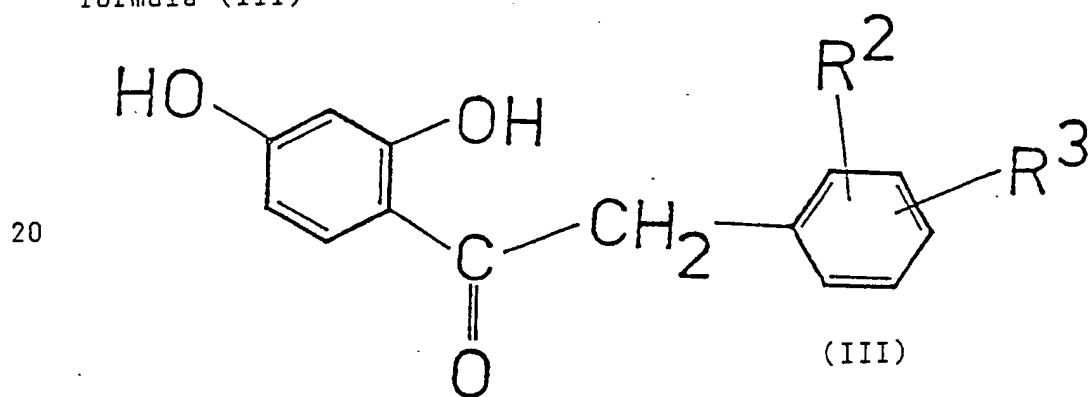
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wherein

R stands for hydrogen or isopropyl,

R² and R³ stand for hydrogen or C₁₋₂ alkoxy -

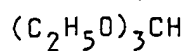
15 by reacting a rezorcinol-derivative of the general formula (III)



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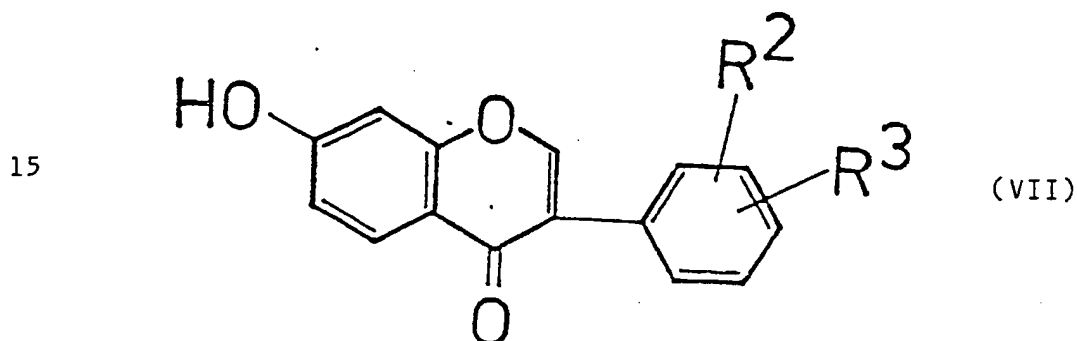
wherein R² and R³ are as given above with ethyl-orthoformate of the formula (IV)

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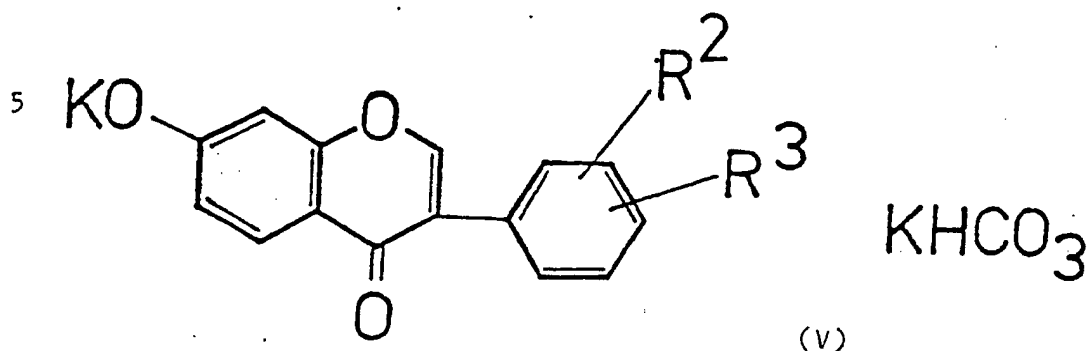
(IV)

in the presence of a base and optionally by alkylating
the product which comprises subjecting the com-
pounds of the general formula (III) and (IV), wherein
 R^2 and R^3 are as given above, to ring-closure at 70-100 °C
5 in the presence of an organic solvent, preferably di-
methyl-formamide and/or isopropanol in a 0.3-2-fold
volume calculated to the volume of the rezorcinol deri-
vatives and/or in the presence of excess of the ester
of the formula (IV) in order to produce a 20-70 % by
10 weight solution (supersaturated) of the product of
the general formula (VII)



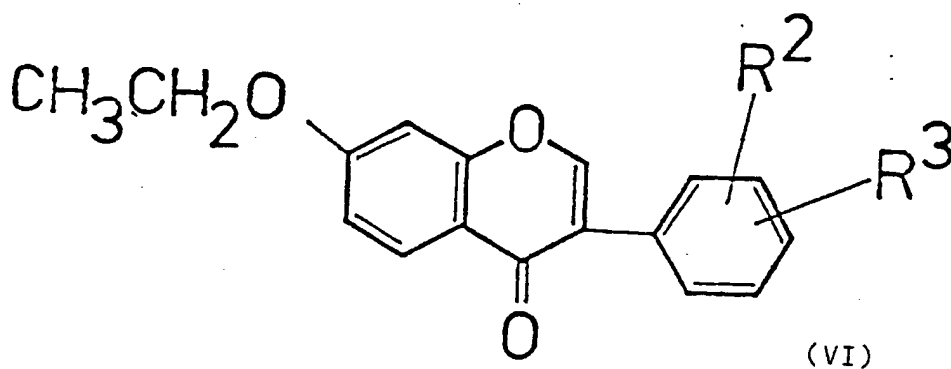
wherein R^2 and R^3 are as given above, and whereby the
20 product of the general formula (VII), wherein R^2 and
 R^3 are as given above, continuously precipitates from
the mixture and filtering the product of the general
formula (VII) after cooling from the reaction mixture
and/or adding a polar or apolar solvent to the reaction
25 mixture and selectively dissolving thus the side product
and filtering the product of the general formula (VII),
wherein R^2 and R^3 are as given above, and/or adding
to the reaction mixture an almost equivalent amount

of anhydrous potassium carbonate and isolating the crystallized double salt of the general formula (V)



10 wherein R^2 and R^3 are as given above, whereafter the products of the general formula (V) or (VII) are reacted with isopropyl-halide and optionally separating the pure product containing at most 0.5 % by weight of

15



20

2. A process as claimed in claim 1 which comprises performing the ring-closure at $80 - 90^\circ\text{C}$

25 by using a heat-treatment for 4-10 hours.

3. A process as claimed in claims 1-2 which comprises retaining ethanol formed in the ring-closing reaction.

4. A process as claimed in claims 1 to 3, which comprises forming the double salt after adding an apolar solvent, preferably toluene to the reaction mixture, and adding anhydrous potassium carbonate at 40 - 80 °C, preferably at 60 °C.

INTERNATIONAL SEARCH REP RT

International Application No PCT/HU 90/00023

I. CLASSIFICATION F SUBJECT MATTER (If several classification symbols apply, indicate all) *		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC ⁵ : C 07 D 311/36; //A 61 K 31/35		
II. FIELDS SEARCHED		
Minimum Documentation Searched *		
Classification System	Classification Symbols	
Int. Cl. ⁵ :	C 07 D 311/36; // A 61 K 31/35	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched *		
AT		
III. DOCUMENTS CONSIDERED TO BE RELEVANT *		
Category *	Citation of Document, ** with indication, where appropriate, of the relevant passages **	Relevant to Claim No. **
A	EP, A2/A3, 0 146 922 (TAKEDA CHEMICAL INDUSTRIES, LTD.) 03 July 1985 (03.07.85), see claims 1,5; page 5, lines 12-15.	(1)
A	DE, A1, 2 640 618 (PFIZER CORP.) 17 March 1977 (17.03.77), see claims 1,3,5,6.	(1,2)
A	DE, A1, 2 640 617 (PFIZER CORP.) 17 March 1977 (17.03.77), see claim 1.	(1,2)
A	Chemical Abstracts, Volume 92, no. 21, issued 1980, May 26 (Columbus, Ohio, U.S.A.), M. C. Beso, "Isoflavone derivatives", see page 638, column 2, the abstract no. 181011x, ES, 477 270.	(1)
A	Chemical Abstracts, Volume 78, no. 15, issued 1973, April 16 (Columbus, Ohio, U.S.A.), Daigo, Koji et al. "4'-Methoxyisoflavon-7-oxyacetic acid and its ethyl ester and analogs", see page 465, column 1, the abstract no. 97484g, JP, 7 246 067.	(1)
<p>* Special categories of cited documents: **</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
14 November 1990 (14.11.90)	21 November 1990 (21.11.90)	
International Searching Authority	Signature of Authorized Officer	
AUSTRIAN PATENT OFFICE	T2a	

Anhang zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

Annex to the International Search Report on International Patent Application No. PCT/HU 90/00023

Annexe au rapport de recherche internationale relatif à la demande de brevet international n°.

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentedokumente angegeben. Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned International search report. The Austrian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche internationale visé ci-dessus. Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsabilité de l'Office autrichien des brevets.

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